

CLAIMS

We claim:

1. A process for preparing leflunomide comprising the steps of
 - a) chlorinating 5-methylisoxazole-4-carboxylic acid by contacting it with a chlorinating agent thereby forming crude 5-methylisoxazole-4-carboxylic acid chloride,
 - b) optionally evaporating excess chlorinating agent or volatile byproducts of the chlorination under reduced pressure, whereby evaporation leaves a residue of unevaporated material containing 5-methylisoxazole-4-carboxylic acid chloride,
 - c) contacting the so-formed crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline in the presence of an alkali metal or alkaline-earth metal bicarbonate in an acylation solvent system comprising at least one solvent component selected from the group consisting of water, ethyl acetate, toluene and dimethyl acetamide, and
 - d) isolating the leflunomide.
2. The process of claim 1 wherein the chlorinating step is conducted in the absence of N,N-dimethylformamide.
3. The process of claim 1 wherein the chlorinating step is conducted in the absence of a catalyst.
4. The process of claim 1 wherein the chlorinating step is conducted neat at a temperature of from about 40° to about 55°C.
5. The process of claim 1 wherein 5-methylisoxazole-4-carboxylic acid is contacted with the chlorinating agent in an inert chlorination solvent at a temperature of from about 50°C to about 80°C.
6. The process of claim 5 wherein the inert chlorination solvent is toluene.
7. The process of claim 1 wherein the chlorinating agent is selected from the group consisting of thionyl chloride, oxalyl chloride, benzoyl chloride, PCl₅ and PCl₃.
8. The process of claim 7 wherein the chlorinating agent is thionyl chloride.
9. The process of claim 1 wherein the at least one solvent component of the acylation solvent system is water.

10. The process of claim 1 wherein the acylation solvent system is a mixture of toluene and water.
11. The process of claim 1 wherein the acylation solvent system is a mixture of toluene and N,N-dimethyl acetamide.
12. The process of claim 1 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with 4-trifluoromethylaniline at a temperature of from about 20°C to about 65°C.
13. The process of claim 12 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with 4-trifluoromethylaniline at a temperature of from about 40°C to about 60°C.
14. The process of claim 1 wherein the crude 5-methylisoxazole-4-carboxylic acid chloride or residue is contacted with from about 1 to about 1.2 molar equivalents of 4-trifluoromethylaniline with respect to 5-methylisoxazole-4-carboxylic acid.
15. The process of claim 1 wherein the alkali metal or alkaline-earth metal bicarbonate is present in from about 1.05 to about 1.2 molar equivalents with respect to the 5-methylisoxazole-4-carboxylic acid chloride.
16. The process of claim 1 wherein contacting the crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline is conducted at a concentration of from about 4 to about 14 volumes of the acylation solvent system per one weight part of 5-methylisoxazole-4-carboxylic acid chloride.
17. The process of claim 16 wherein contacting the crude 5-methylisoxazole-4-carboxylic acid chloride or residue with 4-trifluoromethylaniline is conducted at a concentration of from about 4 to about 14 volumes of the acylation solvent system per one weight part of 5-methylisoxazole-4-carboxylic acid chloride.
18. The process of claim 1 wherein the leflunomide is isolated by precipitation from the acylation solvent system.
19. The process of claim 18 wherein the leflunomide is precipitated at a temperature of from about 0°C to about 25°C.
20. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.

21. The process of claim 20 wherein the leflunomide obtained by precipitation contains about 150 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
22. The process of claim 21 wherein the leflunomide obtained by precipitation contains about 100 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
23. The process of claim 22 wherein the leflunomide obtained by precipitation contains about 50 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
24. The process of claim 23 wherein the leflunomide obtained by precipitation contains about 10 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
25. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide.
26. The process of claim 18 wherein the leflunomide obtained by precipitation is substantially free of N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.
27. Leflunomide prepared by a process comprising the steps of:
 - a) providing 5-methylisoxazole-4-carboxylic acid chloride and
 - b) contacting the 5-methylisoxazole-4-carboxylic acid chloride with 4-trifluoromethylaniline in the presence of an alkali metal or alkaline-earth metal bicarbonate in an acylation solvent system comprising at least one solvent component selected from the group consisting of water, ethyl acetate, toluene and dimethyl acetamide, and
 - c) isolating the leflunomide.
28. The leflunomide of claim 27 wherein 5-methylisoxazole-4-carboxylic acid chloride is provided as crude 5-methylisoxazole-4-carboxylic acid or a residue by:
 - a) chlorinating 5-methylisoxazole-4-carboxylic acid by contacting it with a chlorinating agent to form crude 5-methylisoxazole-4-carboxylic acid chloride and

- b) optionally evaporating excess chlorinating agent or volatile byproducts of the chlorination under reduced pressure, whereby the evaporation leaves a residue of unevaporated material containing 5-methylisoxazole-4-carboxylic acid chloride.
- 29. The leflunomide of claim 27 which is substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
- 30. The leflunomide of claim 29 containing about 150 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
- 31. The leflunomide of claim 30 containing about 100 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
- 32. The leflunomide of claim 31 containing about 50 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
- 33. The leflunomide of claim 32 containing about 10 ppm or less of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide.
- 34. The leflunomide of claim 27 which is substantially free of 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide.
- 35. The leflunomide of claim 27 which is substantially free of N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.
- 36. The leflunomide of claim 27 substantially free of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide, 5-methyl-N-(4-methylphenyl)-isoxazole-4-carboxamide and N-(4-trifluoromethylphenyl)-3-methyl-isoxazole-4-carboxamide.
- 37. A pharmaceutical composition comprising the leflunomide of any of claims 27 through 36.
- 38. A pharmaceutical dosage form comprising the pharmaceutical composition of claim 37.
- 39. A method of treating rheumatoid arthritis comprising administering to a patient in need of such treatment a therapeutically effective amount of the leflunomide of any of claims 27 through 36.
- 40. A method of regulating cell proliferation comprising administering to a patient a an amount of the leflunomide of any of claims 27 through 36 sufficient to inhibit cell proliferation.